

We claim:

1. A method for determining the presence of a target nucleic acid molecule in an biological sample, wherein one of the probe or target biological sample molecules is
5 immobilized comprising:
 - (a) contacting a nucleic acid probe with a biological sample,
wherein the nucleic acid probe hybridizes to a target nucleic acid molecule in the biological sample, and
wherein the nucleic acid probe comprises a crosslinking moiety capable of forming
10 a covalent crosslink between the nucleic acid probe and the target nucleic acid molecule;
 - (b) forming a covalent bond between the nucleic acid probe and the target nucleic acid molecule;
 - (c) washing to remove excess mobile probe or target; and
 - (d) determining the amount of crosslinked nucleic acid probe target complexes.
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2. The method of claim 1 comprising a plurality of different nucleic acid probes and target molecules.
3. The method of claim 1 comprising a plurality of different nucleic acid probes for a
20 single target molecule.
4. The method of claim 1, wherein the biological sample is immobilized.
5. The method of claim 1, further comprising the step of disrupting nucleic acid
25 hybridization within the biological sample.
6. The method of claim 1, wherein the biological sample is a cell, a subcellular structure, a body fluid, or a tissue section.

7. The method of claim 6, wherein said biological sample is fixed on a slide.
8. The method of claim 1, wherein the biological sample is a sample of nucleic acid molecules.
9. The method of claim 8, wherein the sample of nucleic acid molecules is immobilized on nylon membrane or nitrocellulose paper.
10. The method of claim 1, wherein the target nucleic acid molecule is selected from the group consisting of animal, bacterial, fungal, human, parasitic, plant and viral nucleic acids.
11. The method of claim 1, wherein the precursor of the crosslinking moiety is selected from the group consisting of coumarins, furocoumarins and benzodipyrone.
12. The method of claim 1, wherein the precursor of the crosslinking moiety is selected from the group consisting of coumarin, 7-hydroxycoumarin, 6,7-dihydroxycoumarin, 4-methyl-7-hydroxy-coumarin, 6-alkoxy-7-hydroxycoumarin, psoralen, 8-methoxypsoralen, 5-methoxypsoralen, 4,5',8-trimethylpsoralen, 4'-hydroxymethyl-4,5',8-trimethylpsoralen, and 4'-aminomethyl-4,5',8-trimethylpsoralen, a haloalkyl coumarin, haloalkyl furcoumarin, and a haloalkyl benzodipyrone.
13. The method of claim 1, wherein the crosslinking moiety is a mono-adducted furocoumarin:nucleoside adduct.
14. The method of claim 1, wherein the formation of the covalent bond occurs photochemically.

15. The method of claim 1, wherein the formation of the covalent bond occurs chemically.

5 16. In a method for hybridizing a nucleic acid probe to a target nucleic acid molecule in a biological sample, the improvement comprising:

using a labeled nucleic acid probe having a crosslinking molecule capable of forming a covalent crosslink between the nucleic acid probe and the target nucleic acid molecules; and

10 forming covalent bonds between the nucleic acid probe and the target nucleic acid molecule.

17. A method for diagnosing a disease condition in a patient, comprising:

(a) contacting a solution containing a nucleic acid probe to an immobilized
15 sample from the patient,

wherein the nucleic acid probe hybridizes to a target nucleic acid molecule indicative of a disease condition and

wherein the labeled nucleic acid probe comprises a crosslinking moiety which is capable of forming a covalent crosslink between the nucleic acid probe and the target
20 nucleic acid;

(b) forming a covalent bond between the nucleic acid probe and the target nucleic acid molecule;

(c) washing to remove excess, probe or target nucleic acid molecules; and

(d) determining the amount of nucleic acid probe target complexes formed.

25 18. The method of claim 17, further comprising the step of removing nucleic acid probe or target which is not covalently bound, prior to the final step.

19. In a method for hybridizing a nucleic acid probe to an immobilized target nucleic acid molecule, the improvement comprising:

using a nucleic acid probe having a crosslinking molecule capable of forming a covalent crosslink between the nucleic acid probe and the target single-stranded DNA; and

forming covalent bonds between the nucleic acid probe and the target DNA molecule.

20. A kit for determining the presence of a target nucleic acid molecule of an immobilized biological sample, comprising:

a nucleic acid probe having an essentially complementary base sequence to a defined region of the target nucleic acid molecule and having a crosslinking moiety which is capable of forming a covalent crosslink between the nucleic acid probe and the target nucleic acid; and

means for removing nucleic acid probe which is not bound to the target nucleic acid molecule.

21. The kit of claim 20, further comprising means of removing nucleic acid probe which is not covalently bound to the target nucleic acid molecule.

22. The kit of claim 20, further comprising means of labeling said nucleic acid probe.

23. A kit for determining the presence of a target nucleic acid molecule which is immobilized on a nylon membrane or nitrocellulose paper, comprising:

a nucleic acid probe having an essentially complementary base sequence to a defined region of the target nucleic acid molecule and having a crosslinking moiety which

is capable of forming a covalent crosslink between the nucleic acid probe and the target nucleic acid; and

means for removing nucleic acid probe which is not bound to the target nucleic acid molecule.

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24. The kit of claim 23, further comprising means of removing nucleic acid probe which is not covalently bound to the target nucleic acid molecule.

25. The kit of claim 23, further comprising means of labeling said nucleic acid probe.

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26. An array, comprising:

a solid support; and

a plurality of different nucleic acid probes immobilized on said solid support, each nucleic acid probe having a base sequence essentially complementary to a defined region of a target nucleic acid molecule and having a crosslinking moiety which is capable of forming a covalent crosslink between the nucleic acid probe and the target nucleic acid molecule.

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27. The array of claim 26, wherein at least one of the nucleic acid probes is complementary to a target nucleic acid molecule selected from the group consisting of animal, bacterial, fungal, human, parasitic, plant and viral nucleic acids.

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28. The array of claim 26, wherein the crosslinking moiety is selected from the group consisting of coumarins, furocoumarins and benzodipyrone.

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29. The array of claim 26, wherein the crosslinking moiety is selected from the group consisting of coumarin, 7-hydroxycoumarin, 6,7-dihydroxycoumarin, 6-alkoxy-7-hydroxycoumarin, psoralen, 8-methoxypsoralen, 5-methoxypsoralen, 4,5',8-

trimethylpsoralen, 4'-hydroxymethyl-4,5',8-trimethylpsoralen, and 4'-aminomethyl-4,5',8-trimethylpsoralen, a haloalkyl coumarin, a haloalkyl furocoumarin and a haloalkyl benzodipyrene.

5 30. The array of claim 26, wherein the crosslinking moiety is a mono-adducted furocoumarin:nucleoside adduct.

31. A method for determining the presence of a plurality of target nucleic acid molecules in a biological sample, comprising:

- 10 (a) contacting the sample with the array of claim 26, wherein the target nucleic acid molecules hybridize to the immobilized nucleic acid probes;
- (b) forming covalent bonds between the nucleic acid probes and their hybridized target nucleic acid molecules;
- (c) washing the array to remove excess nucleic acid molecules; and
- 15 (d) determining the amount and position of nucleic acid molecules which remain bound to the array.

32. The method of claim 31, further comprising the step of washing the array to remove non-specifically bound nucleic acid molecules.

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33. The method of claim 31, further comprising the step of applying an electric field across the substrate to desorb non-specifically bound nucleic acid molecules.

34. The method of claim 31, further comprising the step of disrupting nucleic acid hybridization within the immobilized biological sample.

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35. The method of claim 31, wherein the formation of the covalent bond occurs photochemically.

36. The method of claim 31, wherein the formation of the covalent bond occurs chemically.

5 37. A method for diagnosing a disease condition in a patient, comprising:

(a) contacting a sample from a patient with the array of claim 26, so that target nucleic acid molecules which are indicative of a disease condition can hybridize to the immobilized nucleic acid probes;

10 (b) forming covalent bonds between the nucleic acid probes and the hybridized target nucleic acid molecules;

(c) washing the array to remove nonspecifically bound nucleic acid molecules; and

(d) determining the amount and position of target nucleic acid molecules which remain bound to the array..

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38. The method of claim 37, further comprising the step of removing nucleic acid molecules which are not covalently bound to the target nucleic acid molecules, prior to the final step.

20 39. A method for genotyping a polymorphic sequence in a patient, comprising:

(a) contacting a solution containing a nucleic acid probe to an immobilized sample from the patient,

wherein the nucleic acid probe hybridizes to a target nucleic acid molecule indicative of a disease condition and

25 wherein the labeled nucleic acid probe comprises a crosslinking moiety which is capable of forming a covalent crosslink between the nucleic acid probe and the target nucleic acid;

- (b) forming a covalent bond between the nucleic acid probe and the target nucleic acid molecule;
- (c) washing to remove excess, probe or target nucleic acid molecules; and
- (d) determining the amount of nucleic acid probe target complexes formed.

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40. The method of claim 39, further comprising the step of removing nucleic acid probe or target which is not covalently bound, prior to the final step.